A. Adverse Event Reports

1. Background

Mandatory Reporting Requirements Applicable to Drugs and Biological Products

FDA regulations and statutory provisions establish adverse event reporting requirements for human drugs, including biological products, and animal drugs. These requirements apply to responsible persons as defined under each provision—generally manufacturers, packers, or distributors of the products in question, as well as holders of approved premarket applications (new drug applications (NDAs), abbreviated new drug applications (ANDAs), new animal drug applications (NADAs), abbreviated new animal drug applications (ANADAs), and biologics license applications (BLAs)), whether or not they also manufacture, pack or distribute.

Drugs for human use and biological products

In general, manufacturers, packers, distributors and applicants with approved applications for new drugs for human use, manufacturers, packers and distributors of licensed biological products, and persons identified on the label as the manufacturer, packer, or distributor of prescription drugs marketed for human use without an approved application are required to submit postmarketing safety reports of adverse drug experiences to FDA.[1] A report of each adverse drug experience that is both serious and unexpected must be made to FDA as soon as possible, but no later than 15 days after receiving information about the event.[2] Persons required to file such 15-day Alert reports are also required to investigate and submit any new information to FDA.[3]

Applicants with approved applications for new drugs or with biologics licenses must also report certain other adverse events to FDA on a periodic basis.[4]

Nonprescription (OTC) drugs marketed without an approved application are also subject to adverse event reporting requirements, under section 760 of the

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[1] 21 C.F.R. §§ 310.305(c); 314.80(c); 314.98 (human drugs), 600.80(c) (biologics). To avoid duplication of reports, non-applicant manufacturers, packers, and distributors of drug and biological products having an approved application may submit all reports of serious adverse drug experiences to the applicant within 5 calendar days of receipt of information about the event, rather than submitting reports to FDA. *See* 21 C.F.R. §§ 314.80(c)(1)(iii), 600.80(c)(1)(iii). Similarly, packers and distributors of prescription drug products marketed for human use without an approved application may meet their postmarketing 15-day safety reporting obligations under 21 C.F.R. § 310.305 by submitting all reports of serious adverse drug experiences to the manufacturer within 5 calendar days of the receipt of information instead of reporting to FDA. Applicants/manufacturers receiving such data must then, in turn, submit a 15-day Alert report to FDA.

[2] 21 C.F.R. §§ 310.305(c)(1); 314.80(c)(1)(i); 314.98(a) (human drugs), 600.80(c)(1)(i) (biologics). There are also certain specific reporting requirements concerning fatalities related to blood and blood products. 21 CFR §§ 606.170(b), 640.73.

[3] 21 C.F.R. §§ 310.305(c)(2), 314.80(c)(1)(ii), 314.98(a) (human drugs), 600.80(c)(1)(ii) (biologics).

[4] 21 C.F.R. §§ 314.80(c)(2), 314.98(a) (human drugs), 600.80(c)(2)(i) (biologics).

Federal Food, Drug, and Cosmetic Act. Manufacturers, packers, or distributors whose name appears on the label of a nonprescription human drug product marketed without an approved application must report serious adverse events associated with their product to FDA within 15 business days.[5]

Animal drugs

For animal drugs, reports of product and manufacturing defects that may result in serious adverse drug events must be submitted by the applicant (or by non-applicant manufacturers, packers, distributors or labelers of the product through the applicant) to the appropriate FDA District Office or resident post within three working days of the company becoming aware that a defect exists.[6] In addition, a report of each adverse drug event that is both serious and unexpected must be submitted to FDA within 15 working days after the applicant first receives information about the event, no matter what the source of the information.[7] Applicants must promptly investigate each adverse drug event that is the subject of a 15-day alert report and provide any significant new information about the event to FDA.[8] Additional drug experience information must be submitted to FDA at periodic intervals—every six months for the first two years following NADA or ANADA approval and yearly thereafter.[9]

Mandatory Medical Device Reporting (MDR) Requirements Applicable to Medical Devices Intended for Human Use

The MDR regulation requires adverse event reporting for manufacturers of medical devices, device user facilities (e.g., hospitals, nursing homes) and importers of medical devices.[10]

Manufacturers of medical devices must submit a report to FDA, no later than 30 calendar days after the day that they receive or otherwise "become aware" of information, from any source, that reasonably suggests that one of their marketed devices (1) may have caused or contributed to a death or serious injury, or (2) has malfunctioned and the device or a similar device marketed by the manufacturer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.[11] Manufacturers of medical devices must also submit a report to FDA no later than five work days after the day that they "become aware" that (1) an MDR reportable event necessitates "remedial action" to prevent an unreasonable risk of substantial harm to public health; or (2) FDA has made a written request for the submission of such a report.[12]

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[5] FDCA §§ 760(b) & (c).
[6] 21 C.F.R. § 514.80(b)(1).
[7] 21 C.F.R. § 515.80(b)(2)(i).
[8] 21 C.F.R. § 514.80(b)(2)(ii).
[9] 21 C.F.R. § 514.80(b)(4).
[10] FDCA § 519, 21 C.F.R. Part 803.
[11] 21 C.F.R. § 803.50(a).
[12] 21 C.F.R. § 803.53.

Importers of medical devices must submit MDR reportable events to FDA, with a copy to the manufacturer, as soon as practicable, but no later than 30 calendar days after the day that they receive or otherwise "become aware" of information, from any source, that reasonably suggests that one of their marketed devices may have caused or contributed to a death or serious injury.[13] Importers must also submit a report to the manufacturer as soon as practicable, but no later than 30 calendar days after the day that they receive or otherwise "become aware" of information, from any source, that reasonably suggests that one of their devices has malfunctioned and that the device or a similar device marketed by the importer would be likely to cause or contribute to a death or serious injury, if the malfunction were to recur.[14]

Device user facilities, which include hospitals, ambulatory surgical facilities, nursing homes, outpatient diagnostic facilities, or outpatient treatment facilities, which are not a physician's offices,[15] must also submit adverse event reports. As soon as practicable, but no more than 10 work days after the day that they "become aware" of information, from any source, that reasonably suggests that a device has or may have caused or contributed to the death of a patient of the device user facility, user facilities must submit a report to FDA and to the manufacturer of the device, if known.[16] User facilities must also submit a report to the manufacturer of the device, if known, and, if the manufacturer is not known, to FDA, no later than 10 work days after the day that they "become aware" of information, from any source, that reasonably suggests that a device has or may have caused or contributed to a serious injury to a patient in their facility.[17] Device user facilities are also required to summarize all reportable events that occurred in the facility during the annual reporting year in annual reports submitted to FDA.[18]

Reporting Requirements Applicable to Dietary Supplements

Manufacturers, packers, or distributors whose name appears on the label of a dietary supplement marketed in the United States must report serious adverse events associated with their product to FDA within 15 business days.[19]

Voluntary Reporting

Anyone can submit reports to FDA about adverse events associated with any FDA-regulated products, including foods, drugs and medical devices. These reports can be submitted in a variety of ways. Adverse events that occur while using medical products (excluding vaccines), conventional foods and dietary supplements, cosmetics, and infant formula can be reported to the

[13] 21 C.F.R. § 803.40(a).
[14] 21 C.F.R. § 803.40(b).
[15] 21 C.F.R. § 803.3 (definition of device user facility).
[16] 21 C.F.R. § 803.30(a)(1).
[17] 21 C.F.R. § 803.30(a)(2).
[18] 21 C.F.R. § 803.33.
[19] FDCA §§ 761(b) & (c).

Agency's MedWatch program. Anyone may report vaccine-related illness or injury to the Vaccine Adverse Event Reporting System (VAERS).[20]

Although FDA requests detailed information about the product and its usage in order to better characterize the adverse event and determine the likelihood it may be caused by the product, adverse event reports vary in the amount of information that can be provided or is known.

In some cases, FDA provides a mechanism for the public to quickly access information from adverse event reports submitted to FDA.

- The Agency's Adverse Event Reporting System (AERS) collects information about adverse events, medication errors and product problems that occur after the administration of approved drug and therapeutic biological products. Individuals familiar with the creation of relational databases can download quarterly (noncumulative) data files from the AERS Web site, including, among other things, the trade name and/or established name of the product, dosage, route of administration, the adverse event, and the health outcome.

- Information about human vaccine adverse events is available online through the Vaccine Adverse Event Reporting System (VAERS).[21] VAERS collects information about adverse events that occur after the administration of vaccines licensed for use in the United States. Public VAERS records include, among other things, the vaccine, dosage, route of administration, the adverse event (including a narrative description), and the health outcome.

- Information about medical device adverse event reports is available online through the Manufacturer and User Facility Device Experience (MAUDE) database. Users can search the database for information on medical devices that may have malfunctioned or caused death or serious injury. Public MAUDE reports include, among other things, the trade name and/or established name of the product, the adverse event (including a narrative description), and the health outcome.

In addition, in some cases, the Agency alerts the public to new information about serious adverse events when it issues communications about an emerging safety issue.

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[20] The National Childhood Vaccine Injury Act requires health care providers to report certain adverse events concerning vaccines through VAERS. 42 U.S.C. § 300aa-25(b).

[21] Vaccines Adverse Event Reporting System, a*vailable at* www.vaers.hhs.gov. The VAERS system is co-sponsored by the Centers for Disease Control and Prevention (CDC) and FDA.

2. Summary of Public Comments

In general, comments from individuals requested disclosure of more information about adverse events that are reported in connection with FDA-regulated products, including information about the type of event, the number of adverse events reported, and/or frequency of occurrence. Comments noted that the information should be provided to the public in an accessible, user-friendly format, and in a timely fashion. One comment urged the FDA to make adverse event reporting systems "straightforward to use" and to make information about adverse events "as easily retrievable as possible."
Some comments wanted FDA to post the frequency of adverse events associated with the use of veterinary products. Some comments noted that it would be helpful to have frequency information provided as a percentage of total adverse events reported; other comments suggested that the number of times an adverse event was reported should be disclosed.

One comment recommended that FDA harmonize and centralize its current adverse event reporting programs, stating that currently, adverse event reports are submitted to the Agency on several Web sites.

Comments that recommended the disclosure of adverse event information stated that public disclosure of adverse events associated with medical products was important to allow users of these products to make informed decisions about these products.

3. Considerations

The Task Force recognizes that there are public health benefits to providing the public with timely information about adverse events reported about FDA-regulated products. Additional disclosure will result in health care providers and patients having access to information that can be used to inform health care decisions.

The Task Force considered the public's interest in FDA providing adverse event information as soon as practicable, and even when the Agency has not determined whether the adverse event is likely associated with product. The Task Force considered the risk that the public may draw assumptions and possibly conclusions about a product based on incomplete information. The Task Force also considered that it is important for FDA to be transparent about the limited usefulness of adverse event reports that are disclosed when FDA has not analyzed their association to the FDA-regulated product. The Task Force considered whether, if preliminary information from adverse event reports is disclosed, a disclaimer should be included that cautions the public about drawing conclusions about products based solely on adverse event information because there is no certainty that the reported event was actually caused by the product and reports do not always contain enough detail to fully evaluate an event.

The Task Force also took into account the fact that although certain entities (generally manufacturers, packers, distributors and in some cases user facilities) are required to submit adverse event reports, other persons, including, in most cases, health care providers and patients, report adverse events voluntarily. Thus, there is no way of knowing the actual number of adverse events that may be associated with a product because of under-reporting. FDA also does not know the actual number of people or animals that have been exposed to a product because sales data and other available proprietary product distribution information, the best estimates available to FDA, do not necessarily equate to product use. The Task Force considered whether it would be misleading to disclose the frequency of adverse events reported as a percentage of total adverse events reported for a product or as a percentage of the exposed population. FDA does not receive information about all adverse events and may not have accurate data about the number of people or animals that are exposed to the product, which is necessary to calculate accurately the frequency of adverse events for an exposed population.

The Task Force considered the Agency's current capability to quickly process adverse event reports for disclosure to the public. Regardless of any system used, adverse event reports (i.e., individual case safety reports (ICSRs)) must be reviewed for quality control purposes, entered into the system, and non-public information such as personal information redacted (e.g., name of the patient, or any other information that would identify the patient) before the ICSR describing the adverse event can be disclosed to the public.

4. Draft Proposal(s) for Public Comment

DRAFT PROPOSAL 1:

FDA should expand the areas in which it provides the public with online access to public information from adverse event reports about FDA-regulated products submitted to FDA, in a format that is searchable and allows users to generate summary reports of this information, including, if known and as applicable, the trade name and/or established name of the product, dosage, route of administration, description of the adverse event, and the health outcome. Adverse event report information should continue to be disclosed with a clear disclaimer about the limits of the information.

Reasoning: Individuals using, or who have an interest in using, an FDA-regulated product have a particular interest in receiving information about the safety of that product as soon as possible. For medical products, for example, this information can be used by prescribers, patients, public health officials, and consumers to inform decisions about the use of such products, and may

help those who use the product to identify and report additional adverse events.

Public access to adverse event reports can provide industry with more complete information that can be used to assess the safety profile of products and may help industry determine more quickly whether additional actions are required to ensure the safe use of a product.

FDA is likely to have the most complete database of adverse event reports about a particular product because of the reporting systems described above. Making adverse event report information about FDA-regulated products more accessible to the public provides a window into FDA's post-marketing surveillance system. Disclosing some of the data FDA uses to monitor FDA-regulated products once they are on the market may lead to better understanding of the post-marketing surveillance system.

FDA has some experience providing the public with online access to adverse event report information quickly, as discussed in section 1 above. But in many circumstances, members of the public only have access to information from adverse event reports by submitting a Freedom of Information Request (FOIA) request to FDA. This method does not provide broad access to the information nor is it efficient for Agency employees to provide this public information on a piecemeal basis.

FDA should provide adverse event reports for all FDA-regulated products in a similar manner. There is no compelling reason for providing differential access to adverse event reports for FDA-regulated products. FDA should aim to provide the public with increasing availability and accessibility of adverse event report information for all FDA-regulated products. Increased availability of this information can arm the public with information relevant to the safe use of products, free up Agency resources for other activities that improve public health, and further the goals of the Administration in achieving more transparent government.